

Claims 4, 6 and 24 have been canceled and Claims 1 and 19 have been amended to incorporate the subject matter of originally filed Claims 6 and 24.

Claims 1-3, 11-19 and 28-30 have been amended to more particularly point out and distinctly claim that which Applicants regard as their invention.

Support for this Amendment can be found at page 6, lines 17-23, page 21, lines 5-9, and at page 20, line 2 and page 21, line 15 to page 22, line 12.

New Claim 39 had been added to claim one embodiment of Applicants' invention. Support for new Claim 39 can be found at page 22, lines 14-19 and in the originally filed Claim 31.

No new matter has been introduced.

The remaining portion of this reply is set forth under appropriate subheadings for the convenience of the Examiner.

#### Advantages of Applicants' Invention

Applicants invention pertains to particles which are particularly advantageous in pulmonary delivery. Among other features, the particles combine the benefit derived from their mean particle diameter, which is sufficiently large to evade phagocytic engulfment by alveolar macrophages, with the benefit derived from their aerodynamic diameter which is sufficiently small for successful delivery to the deep lung and the central and peripheral airways. A detailed discussion of these and other features characterizing Applicants' particles is found in the specification at page 16, line 25 through page 17, line 15.

#### Rejection under 35 USC §102(b) over Illum, U.S. Patent No. 4,904,479

Claims 1-5, 9 and 14 are rejected under 35 USC §102(b) over Illum, U.S. Patent No. 4,904,479. The Examiner states that Illum teaches polystyrene microspheres of 5.25 micrometers coated with polyoxamer, that the intended use has no patentable significance in composition claims and that, in the absence of showing otherwise, it is deemed that Illum's microspheres have the claimed density.

Applicants respectfully disagree. Illum discloses polystyrene microspheres coated with a polyoxamer coat having a thickness of about 100 Ångstroms or more. The polyoxamer coat is a key feature in the Illum particles and is relied upon to prevent phagocytic uptake by peritoneal

macrophages. Column 4, line 49 through column 5, line 11. In contrast, Applicants' claimed invention, as amended, does not embrace such particles.

Illum discloses injecting the coated microspheres. Contrary to the position taken by the Examiner, the intended use of the particles disclosed in the reference indicate that there is no recognition in Illum of the problems associated with pulmonary delivery to the deep lung which are addressed by Applicants. The reference does not teach or suggest aerodynamically light particles. No disclosure or suggestion is made touching upon the tap density of the particles employed in Illum nor upon their aerodynamic diameter. No teaching or suggestion is present in Illum regarding particles which have a tap density of less  $0.4 \text{ g/cm}^3$ , a mean diameter between 5 and 30 microns and an aerodynamic diameter between approximately 1 and 5 microns.

Accordingly, Applicants respectfully submit that Applicants' claimed invention is patentable in view of Illum.

#### Rejection under 35 USC §102(b) over Yen, U.S. Patent No. 5,069,936

Claims 1, 4, 6, 9-14 are rejected under 35 USC §102(b) over Yen, U.S. Patent No. 5,069,936. The Examiner states that Yen teaches protein microspheres containing a surfactant as polyoxamer, that the intended use has no significance in composition claims and that in the absence of showing otherwise, it is deemed that Yen's microspheres have the claimed density.

The microspheres taught by Yen have particle sizes in the range of 0.01 to 5 microns. (Column 9, lines 65-66.) The small size enables their "passage through even capillaries". Column 1, lines 55-56. Yen does not disclose or suggest aerodynamically light particles having Applicants' mass mean diameter, tap density and aerodynamic diameter. Contrary to the position taken by the Examiner, Applicants respectfully submit that the intended use of the particles disclosed in Yen for injection underscores the fact that there is no recognition in Yen of particle properties that enhance delivery to the deep lung or to the central and peripheral airways. Thus, there is no teaching or suggestion in Yen to make particles having a tap density less than  $0.4 \text{ g/cm}^3$  and an aerodynamic diameter between approximately 1 and 5 microns, such as the particles claimed by Applicants.

The ideal microspheres taught by Yen have diameters between 0.05 to 0.5 microns. (Column 14, lines 22-39.) Such particles, however, are not suited for delivery to the deep lung since they tend to be re-breathed or exhaled. See, for example, Baichwal, U.S. Patent No. 5,612,053 at column 4, lines 45-46. Furthermore, the selection of the upper diameter limit of the

microspheres in Yen is at least partly based on the fact that microspheres greater than 0.5 microns can easily be phagocytized by macrophages in the body. See column 14, lines 22 - 28. In contrast, Applicants' claimed invention describes particles which, as stated at page 17, lines 3-15 of the subject application, are too large for the cytosolic space required within a macrophage for complete particle phagocytosis.

In view of the above, Applicants respectfully submit that their claimed invention is patentable in view of Yen.

Rejection under 35 USC §102(e) over Baichwal, U.S. Patent No. 5,612,053

Claims 1-5, 9-15, 17-20, 24-30 and 32-33 are rejected under 35 USC §102(e) over Baichwal, U.S. Patent No. 5,612,053.

The Examiner states that the diameters of the particles taught by Baichwal encompass the diameters of the present particles.

However, the reference does not teach or suggest aerodynamically light particles having a tap density of less than 0.4 g/cm<sup>3</sup> or and an aerodynamic diameter between approximately one and five microns. In addition, the cohesive composite particles disclosed in Baichwal require the presence of a polysaccharide gum. Such compositions are not embraced by Applicants' claimed invention.

Accordingly, Applicants respectfully submit that their claimed invention is patentable under 35 USC §102(e) over Baichwal.

Rejection under 35 USC §103(a) over Baichwal, U.S. Patent No. 5,612,053

Claims 1-33 are rejected under 35 USC §103(a) over Baichwal, U.S. Patent No. 5,612,053, in view of Applicants' statements of prior art.

The Examiner states that the preparation of Baichwal's particles with the tap density of the present particles would have been obvious to one of ordinary skill in the art.

Applicants respectfully disagree. There is no recognition in Baichwal of problems associated with phagocytosis. Baichwal, in fact, teaches particles having a mass mean diameter of about 2 microns for administration to the alveoli of the lungs. Such particles are susceptible to phagocytosis.

Furthermore, none of the prior art references, including the prior art described on pages 10 and 15-17 of the specification, describe particles consisting of the agent and surfactant or the

agent and charged molecule with the mass mean diameter size, tap density and aerodynamic diameter of the claimed particles. The advantages of this novel class of particles for pulmonary delivery have not been described in the prior art.

Applicants acknowledge the Examiner's request for copies of the references cited in the application. These references are also cited in the Information Disclosure Statement, filed by Applicants on January 7, 1999 and, thus, are believed to be available to the Examiner.

Rejection under 35 USC §103(a) over Masinde (International J. of Pharmaceutics) in view of Illum, U.S.. Patent No. 4,904,479

Claims 1-33 are rejected under 35 USC §103(a) over Masinde (International J. of Pharmaceutics) in view of Illum, U.S.. Patent No.4,904,479, optionally in further combination with Applicants' statements of prior art.

The Examiner states that Masinde discloses polylactic acid microspheres with a mean diameter of 12.1 microns and aerodynamic diameter of 2.1 microns. The Examiner relies on Illum to teach the addition of surfactants.

Masinde is directed to aerosolized aqueous suspensions of poly(L-lactic acid) microspheres. The second paragraph in the *Introduction* section of Masinde highlights disadvantages associated with dry powder inhalers in comparison with the particle suspensions by nebulizers, addressed in Masinde.

There is no suggestion in Masinde, a reference directed to aqueous suspensions of microspheres, that it be combined with Illum (optionally in further combination with Applicants' statements of prior art), as stated by the Examiner. Absent such a suggestion, there would be no reason why one skilled in the art, faced with the problems faced by Applicants and without prior knowledge of Applicants' invention would consult the particular combination of references suggested by the Examiner.

In fact, Masinde teaches away from Applicants' invention. As stated, for example, at page 18, lines 21-24, of the subject application, tap density is diminished by particles surface irregularities and particle porosity. It is one of the advantages of Applicants' invention to deliver to the lung particles which have a mean particle diameter larger than the mean aerodynamic diameter. See also discussion and the formulae on page 19 the subject application. In contrast, as stated in the summary in Masinde and seen in the scanning electron micrographs figures, the microspheres in Masinde are "round and smooth". Furthermore, Table 1 reveals that the

Masinde particles have a median diameter of 4.2 microns and a mean aerodynamic diameter of 4.6 microns.

Accordingly, it is submitted that Claims 1-33 are patentable over Masinde in view of Illum, optionally in further combination with Applicants' statements of prior art.

#### CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance and it is respectfully requested that the rejections be reconsidered and withdrawn and the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (781) 861-6240.

Respectfully submitted,

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

By 

Carolyn S. Elmore

Registration No. 37,567

Telephone (781) 861-6240

Facsimile (781) 861-9540

Lexington, Massachusetts 02421-4799

Dated: 6/21/99